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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,352	10/08/2003	Kyoji Ogoshi	3190-044	8311

33432 7590 02/24/2006

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EXAMINER	
TALAVERA, MIGUEL A	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/681,352	OGOSHI, KYOJI	
	Examiner	Art Unit	
	Miguel A. Talavera	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on July 1, 2005), Applicants filed a response and amendment received on September 26, 2005. Said amendment cancelled claims 15-18, added new claims 19-24 and amended claims 1, 4-7, 11 and 13. Rejections and/or objections not reiterated from the previous non-Final rejection are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied to the instant application.

Priority

2. The instant application is a continuation of PCT/JP02/02894 filed on March 26, 2002. The benefit of priority is not granted for the two foreign applications filed in Japan as requested in the declaration because the instant application does not comply with the rules set out in 35 U.S.C. § 119 (a)-(d): namely, a certified copy of the original foreign application has not been filed with the Office. Applicants are requested to comply with these rules, if possible, or withdraw claims to priority benefits. Therefore, this Office action considers prior art before the earliest effective filing date of March 26, 2002

Information Disclosure Statement

3. As previously noted, the information disclosure statements provided by Applicants (filed on October 8, 2003 and December 18, 2003) have been considered.

NEW-Claim Objections

4. Claims 1-14, 20 and 23 are objected to for the improper use of numbers within the claims. Specifically, claims 1, 7, 11, 13, 20 and 23 itemized sequence steps by using integers (i.e., 1, 2, etc.) that are usually reserved for claims. It is suggested that sequence steps be distinguished by using other sequential characters such as, a, b, c or i, ii, iii, etc.

5. Claim 7, 9 and 10 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 requires the contacting a compound with a three-dimensional structure, establishing/evaluating an interaction and detecting a signal of the interaction, which is not a narrower limitation of claim 1 (step 5) that requires the screening of a compound. That is, claim 1 requires the examination or testing of a group of compounds to separate those who interact from those who have a defective characteristic preventing interaction, wherein discrimination of compounds necessitates detecting a signature signal for interaction. Claims 9 and 10 are not narrower limitations of claims 1 and 7, respectively; as the limitations of both claims 9 and 10 have been already established in claim 1 (step2).

Applicant is advised that should claims 1 and 2 be found allowable, claims 7-10 will be objected to under 37 C.F.R. § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k).

6. Claim 7, 9 and 10 are objected to for the following informalities:

a. Claim 7 is objected to because is missing a conjunction linking step (1) and step (2). Examiner suggests inserting ---and--- or ---or--- after the recitation of "....structure is possible,". In addition, the **comma** after the recitation of "compounds" in step (2) is inappropriate. Either the creation of an additional step (i.e., step 3) reciting "detecting a signal of the interaction" or the removal of said comma is suggested by examiner so that both "evaluating the interaction....compounds" and "detecting a signal of the interaction." are part of step (2).

b. Claims 9 and 10 is objected to because of typographical errors. The comma after the recitation of "HLA" is inappropriate. In both instances, the removal of said comma is suggested.

NEW-Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 1-14 and 19-24 are rejected under 35 U.S.C. § 1 12, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1 (steps 2 and 3), 11 (steps 2 and 3), 13 (steps 2 and 3), 19, 20 (steps 2 and 3), 21 and 23 (step 2) recite "analyzing variation", "determining variation" or "polymorphic variation". However, the specification does not define how such "variation" is to be determined. To clarify the record, the reference of Rigas, B. (Gastroenterology, vol. 111, pp. 523-526, 1996) teaches that:

> "Each locus (i.e., HLA-DQ, -DP, and -DR) in the HLA chromosomal region is occupied by an allele. That many alleles (versions of the same gene) can occupy a given locus leads to the polymorphism of HLA genes. In some instances, more than 100 such allelic variants have been described. HLA alleles were initially identified by serological typing and designated by a letter denoting the locus followed by a number, e.g., HLA-B27. Application of the polymerase chain reaction to HLA typing revealed even greater polymorphism based on allele DNA sequence; the price for this development was more cumbersome terminology, e.g., DQB1*0301 refers to the 0301 allele of the HLA-DQB1 locus." (see p. 524 and Figure 1)

Accordingly, there are 59 alleles in locus HLA-DPB1, 26 alleles in locus HLA-DQB1 and 106 alleles in locus HLA-DRB1: total of 191 alelles that could potentially encode the β chain of an HLA class II polypeptide. Therefore, is this determination of "variation" based upon analysis of a single HLA DRB1* allele, analysis of multiple HLA DRB1* alleles or analysis of an HLA DRB1* allele and other HLA alleles, i.e., HLA-DPB1*? Clarification is required.

9. Claims 1-10 fail to accomplish the preamble of "determine effective cancer treatment", which is not done *in silico* as required by step (5) of claim 1. Similarly, claims 4-6 can not be

accomplished *in silico*. Claim 7 is also done *in silico* and fails to accomplish preamble of independent claim.

10. Claims 2, 8, 12, 14, 21 and 24 are dependent claims of methods for screening a "cancer treatment medicine" (see claim 1 and 7) and evaluating "anticancer treatments" or "cancer treatments" (see claim 11 and 13). Said claims recite the phrase "wherein cancer is analyzed by distinguishing stomach cancer from other cancers". However, the corresponding independent claims do not provide any methods steps for how such analysis of distinguishing cancer types is accomplished. Thus, the lack of method steps in claims 1, 7, 11 and 13 addressing discrimination between cancer types makes claims 2, 8 and 14 confusing. Similarly, claims 21 and 24 recite said phrase and depend on claims to a composition (see claims 19 and 23), wherein no clear indication of such analysis for discriminating cancer types is apparent. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is practiced. The method steps should at least include a correlation step describing how the results of identifying a particular polymorphic variant, identifying a compound that interacts with the three-dimensional structure of said variant and distinguishing cancer types allows for the determination of a medicine or the evaluation of a treatment. Clarification is required.

11. Claim 3 is indefinite in the recitation of the "the three-dimensional structure of the candidate compounds". There is a lack of antecedent basis for this recitation in the claim.

12. Claim 7 (step 1) recites the phrase "variation of each amino acid", which is unclear as to the limitations it imparts on the claimed subject matter or as to what said phrase encompasses. The specification provides no clear definition of what is intended by this phrase. What is

encompassed by said variation? Is it variation of the chemical identity of amino acid? Is it variation of sidechain rotamers, i.e., conformations of amino acid? Furthermore, which amino acids would be affected by said variation? All the amino acids in the polypeptide sequence? Or just the identified polymorphic positions in the polypeptide sequence? Clarification is required.

13. Claim 7 (step 2) recites the phrase "detecting a signal of the interaction", which is unclear as to the limitations it imparts on the claimed subject matter or as to what said phrase encompasses. The specification provides no clear definition of what is intended by this phrase. What is the signal being detected in the computer-assisted step of docking compounds? Steric hindrance? Electrostatic complementarity? Compound induced conformational changes? Clarification is required.

14. Claims 22 (claims 23 and 24 dependent therefrom) is confusing in the recitation of "a polymorphic variation of a DRB1*gene, DQB1*gene, and DPB1*gene of HLA". The claim is drawn to a composition comprising an isolated polypeptide. However, the metes and bounds of said recitation are unclear. Does it mean a composition comprising all polymorphic variation of the β chain (i.e., a total of 191 polypeptides), three β chain polypeptide variations encoded by one allele from three HLA loci (i.e, HLA-DQB1, -DPB1, and -DRB1) or a single β chain polymorphism encoded by a single allele? Clarification is required.

15. Claim 22 recites the "polypeptide encoding a polymorphic variation of a DRB1* gene, DQB1* gene, and DPB1* gene of HLA", which is unclear as to the limitations it imparts on the claimed subject matter or as to what said phrase encompasses. Initially is noted that polypeptides do not encode for nucleic acids. Only nucleic acids encode for polypeptides.

Clarification is required. For the purpose of examination the recitation has been interpreted as --- polypeptide encoded by a polymorphic variation of...---.

16. Claim 24 is confusing because it refers to "the method according to claim 23". However, claim 23 is drawn to "the composition of claim 22". Clarification is required.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

NEW-*Writtten Description*

Claims 1-14 and 19-24 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant ad that the inventor(s), at the time the application was filed, had possession of he claimed invention.

17. Claims 1-10 are drawn to a screening method for effective cancer treatment medicines based on analyzing a genus of polymorphic HLA genes, DRB1*, DQB1* and DPB1* (herein referred as HLA class II polymorphic genes), and encoded polypeptides thereof, in patients cared by treatments consisting of surgery by itself or surgery in combination with either chemotheraphy or immunotheraphy, and identifying a polymorphic variant that has a statistical

significant relationship with at least one of the treatments, wherein the identified polymorphic variants are used to generate a genus of three-dimensional structures, which are ultimately use for *in silico* screening of compounds that upon interaction with the three-dimensional structure might have the potential of being a "cancer treatment medicine". To clarify the record, the specification does not define what "creating a three-dimensional structure" means. For the purpose of examination, the examiner has interpreted such recitation as providing all possible three-dimensional structures/models of the identified polypeptides encoded by said genus of polymorphic HLA class II genes, wherein the structures are generated either by computational methods or by X-ray crystallographic analysis. Accordingly, included in this widely variant genus are three-dimensional structures of distinct compositions associated with the polymorphism imparted by the genetic source.

18. Claims 11-14 are drawn to a measuring method for evaluating anticancer treatments or for evaluating cancer treatments relying on the determination of one position of a polymorphic amino acid in a polypeptide sequence encoded by at least one species of a genus of HLA class II polymorphic genes, in patients cared by treatments consisting of surgery by itself or surgery in combination with either chemotheraphy or immunotheraphy, and identifying a polymorphic variant that has a statistical significant relationship with at least one of the treatments, wherein either the amino acid sequence or the base sequence of the species having statistical significant relationship with at least one of the treatments is determined.

19. Claims 19-24 are drawn to a composition comprising an isolated polypeptide having an amino acid sequence encoded by at least one species of a genus of HLA class II polymorphic genes, wherein polymorphic variation has a statistical significance with a cancer treatment.

For claims drawn to a genus, M.P.E.P. § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. M.P.E.P. § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus.

Further, the Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

Regarding the methods of claims 1-14, *University of Rochester v. G.D. Searle & Co.* (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v. G.D. Searle & Co.* the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from *Enzo Biochemical* (see above).

Polynucleotides and encoded polypeptides thereof

Claims 1-14 and 19-24 encompass methods of using and compositions comprising a genus of HLA class II gene/polynucleotides encoding a genus of polymorphic variants of HLA class II polypeptides having a statistical relationship with a cancer treatment. However, the specification lacks a clear and concise structural and functional correlation for the claimed genera. Although Applicants seem to establish that the HLA class II encoded polypeptides encompassed by the broad claims are full-length HLA class II polypeptides consisting of a heterodimer between an invariant α chain and a polymorphic β chain, there is no clear description (i.e., SEQ ID identifier, number of amino acid residues or nucleotides, etc). As noted in item #8, multiple human variants of HLA class II exist in nature, more could be generated in the lab, and the claims are not limited to specific polymorphic variants. Without identifying and sequencing each one, there is no way to know what their sequences are. Therefore, applicants have not disclosed, nor does the art recognize, the requisite structural and functional features of all the contemplated nucleic acid and amino acid sequence possibilities recited in the instant claims, which result in the disclosed statistical significant relationship with a cancer treatment, a feature deemed essential to the instant invention. Furthermore, the prior art (Gorski et. al. J. Immunol., vol. 143, pp 329-333, 1989), regarding polymorphic regions of HLA class II genes, teaches:

> "In HLA class **II** molecules (HLA-DR, -DQ, -DP), the polymorphism was shown to be predominantly found in the N terminal first domain [**1**). The first molecular cloning and sequencing results supported this observation. Many recent sequence analyses of HLA class **II** polymorphism have restricted themselves to the more polymorphic first domain on the basis of the previous argument. In addition, if the structure of the class **II** molecules is similar to that of class I (2), then the second domain cannot be expected to participate directly in MHC-Ag or MHC-TCR

> contacts. However, polymorphisms in the second domain can be the target of a humoral response and thus may be important."

Neither the specification nor claims as written make such distinction between two polymorphic domains involve in distinct functions. There are no descriptions of variable regions in the polynucleotide or the encoded polypeptide that correlate with a statistical significant relation ship with a cancer. As such a skilled artisan would not recognize which polymorphic domains are essential for practicing the claimed invention. Specifically, which regions of the polypeptide are useful to screen for "cancer treatment medicines", a feature essential to generate suitable screening 3D-models representative of the encoded polypeptides. One of skill in the art would recognize that Applicant was not in possession of the entire genus of polymorphic HLA genes, DRB1*, DQB1* and DPB1*, and encoded polypeptides thereof.

Three-dimensional models: In this case claims 1-10 rely on the creation of a three-dimensional structure/model of a genus of polypeptides encoded by HLA genes, DRB1*, DQB1* and DPB1* having a statistical relationship with a cancer treatment. Because the genus of polypeptides encoded by HLA genes, DRB1*, DQB1* and DPB1* is not adequately described, it follows that a model derived from said genus of polypeptides encompasses a population of species widely variant in structure and atomic composition. Initially, it is noted there is no description of any "created three-dimensional structure". Secondly, it is also noted that the three-dimensional structure/models are limited to the polymorphic β chain and not the HLA class II heterodimer. In the event that the structural coordinates of said genera of polypeptides are required to practice the claimed method (i.e. creating a three-dimensional structure), applicants have failed to describe all possible crystals forms containing the claimed genera of polypeptides that are

necessary to obtain said structural coordinates. The specification does not describe any crystal containing the claimed genera of polypeptides that, upon X-ray crystallographic analysis, would lead into a set of structural coordinates for any species of the claimed genera. The skilled artisan would recognize said crystal forms as critical for the determination of the structure factor phases of a species from the claimed genus, regardless of the art-recognized phasing methods (i.e. molecular replacement, direct methods, isomorphous replacement, anomalous dispersion, etc) envisioned for this purpose. In turn, said structure factor phases are essential for calculating an electron density map and rendering the structural coordinates necessary to generate any of the species within the genera of three-dimensional models. No such description exists in the specification for any representative species of the claimed genera of polypeptides to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of structural coordinates of all possible polypeptides of the claimed genera. There are no requirements as to whether the models have atoms that are covalently attached or separated by a distance within the radius of gyration of the polypeptide, only that the models are generated with a polypeptide encoded by at least by HLA genes, DRB1*, DQB1* and DPB1*, i.e., β chain, having at least one polymorphic amino acid that has been correlated to a cancer treatment.

As a consequence of all the reasons given above, the disclosure is insufficient to be representative of the attributes and features of all species encompassed by the recited genera of the claims. Given the lack of description of a representative number of polymorphic polynucleotides and encoded polypeptides thereof, a representative number of crystals containing species of the claimed genus of polypeptides and a representative number of three-

dimensional models, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention. A description of what a material does (i.e., HLA class II polymorphic loci encoding for polypeptides having promiscuous antigenic peptide recognition attributed to genetic polymorphism) rather than of what it is, usually does not suffice. The instant application does not more than describe the function of the HLA Class II polypeptides and contains no information by which a person of ordinary skill in the art would understand that the inventors possessed crystals consisting of the claimed genus all HLA class II encoded polypeptides having a significant relationship with a caner treatment. At best, it simply indicates that one should run tests on a wide spectrum of **polymorphic alleles** in the hope that at least one of them can be isolated, crystallize and lead to a suitable screening three-dimensional model. Inadequate written description that merely identifies a plan to accomplish an intended result "is an attempt to preempt the future before it has arrived" (*Fiers v. Revel*, 984 F.2d 1164,1171 9Fed.Cir. 1993).

New-Scope of Enablement

20. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for *in silico* screening of compounds using a homology model of an entire HLA heterodimer structure (or a defined binding pocket within said model), does not reasonably provide enablement for making new crystals from which a three-dimensional model could be generated or homology modeling with the β chain of an HLA heterodimer. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. To practice the claimed methods to the full extent of their scope would require undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See M.P.E.P. § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: Claims 1-10 are so broad as to encompass computer-based screening methods for analyzing the interaction of a candidate anticancer compound with a three-dimensional structure of polypeptide encoded by at least one HLA class II gene that require the generation of all possible three-dimensional models using any suitable technique in structural biology. Accordingly, said models could be generated through X-ray crystallographic analysis or computational modeling methods not requiring X-ray diffraction data, such as comparative/homology modeling, relying on protein sequence information. The broad scope of claimed models is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides variants encoded by HLA Class II genes for X-ray crystallographic analysis, including all potential crystals, crystallization conditions and experimental models thereof necessary for such analysis. In this case the disclosure is limited to:

> "Methods of drug designing by comparison of the three-dimensional structures of the candidate compounds, based on the three-dimensional structures and each amino acid's positions and variations, are provided."(see specification, p.10) .

Thus, the support is limited to drug design methods necessitating comparison of the three-dimensional structure of several compounds but do not require the three dimensional structure of the protein target, such as pharmacophore-based virtual screening methods (for a review, see Hou *et al.* Curr. Pharmaceut. Design vol. 10, pp. 1011-1033). However, the claimed screening method requires "creating a three-dimensional structure of a least one amino acid sequence" encoded by at least one of DRB1* gene, DQB1*gene, and DPB1*gene of HLA, i.e, polymorphic variants of β chain.

The nature of the invention: The invention is related to screening for compounds that interact with a three-dimensional structure/model of a protein that is generated either from X-ray diffraction data or amino acid sequence data. For the reasons discussed below, the nature of the claimed invention is highly complex.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art:

Models generated through X-ray diffraction data of a macromolecular crystal

The state of the art at the time of the invention acknowledges a high level of unpredictability for making the full scope of the three-dimensional model/structures obtained through the crystallization and X-ray diffraction analysis of the polypeptides claimed in the method. It is well known in the art of protein chemistry that crystallizing a macromolecule is a chancy and difficult process without any clear expectation of success. It is now evident that protein crystallization is the main hurdle in protein structure determination. For this reason,

protein crystallization has become a research subject in and of itself, and is not simply an extension of the structural biologist or crystallographer's laboratory. There are many references that describe the difficulties associated with growing protein crystals. See for example, Kierzek *et al.*, Biophys. Chem., vol. 91, pages 1-20, 2001, Wiencek, Annu. Rev. Biomed. Eng., vol. 1, pages 505-534, 1999 and Ke & Doudna, Methods, vol. 34, pp. 408-414, 2004.

> "Crystallization is predictably the least predictable aspect of a structure determination project" (see Ke & Doudna, page 408)

It is commonly held that crystallization of macromolecules from solution is the major obstacle in the process of determining macromolecular structures. The reasons for this are many; biological macromolecules are complex, and the delicate balance involving specific and non-specific interactions with other macromolecules and small molecules in solution, is difficult to predict.

Each biological macromolecule crystallizes under a unique set of conditions, which cannot be predicted in advance. Simply supersaturating the macromolecule to bring it out of solution may not work, the result would, in most cases, be an amorphous precipitate. Many precipitating agents are used, common ones are different salts, and polyethylene glycols, but others are known. In addition, additives such as metals and detergents can be added to modulate the behavior of the macromolecule in solution. Many kits are available (e.g. from Hampton Research ©), which attempt to cover as many parameters in crystallization space as possible, but in many cases these are just a starting point to optimize crystalline precipitates and crystals which are unsuitable for diffraction analysis. Likewise, known crystallization conditions of another macromolecule with sequence identity or similar fold as the target macromolecule for

crystallization are also often regarded as a starting point of parameters in crystallization space. Successful crystallization is aided by knowledge of the macromolecules behavior in terms of solubility, dependence on metal ions for correct folding or activity, interactions with other molecules and any other information that is available. As evidence by Derewenda *et al.* (Acta Crystallogr. D., vol. 62, pages 116-124, 2006) the outcome of macromolecular crystallization is further compounded by the chemical composition of the macromolecule itself, in particular the molecular surface area, and available surface sites that might participate (i.e., crystal contacts) in holding together the three-dimensional array of macromolecules defining the crystal lattice:

> "Clearly, the protein's microscopic surface properties have a critical impact on the thermodynamics and kinetics of crystallization. It follows then that some proteins will crystallize more easily than others and that the amino-acid composition and sequence are more informative with respect to possible crystallization outcome than is normally believed."(see Derewenda *et al.*)

Because functional variants within the claimed polypeptide genus, might differ primarily in their molecular surfaces, said functional variants are unpredictable to crystallize because one can not predict the particular juxtaposition of functional groups of neighboring molecules that would lead to crystal contacts.

> "It is arguable that homolog screening is a relic of the bygone era when it was the only means of diversifying the protein sample. In reality, it suffers from a major limitation: the crystallizability of any given homolog is as unpredictable as that of the original target." (see Derewenda *et al.*)

It is noted that the polypeptides encoded by HLA Class II genes are polymorphic glycoproteins (see specification, p.5, last five lines). Thus, it was also well known in the art that the specific chemical composition and glycosylation state of a protein largely defines crystallization success and the corresponding macromolecular crystal of a glycoform, such as those encoded by at least one HLA Class II gene. The general knowledge in the art, as

exemplified by Buts *et al.* (Acta Crystallogr. D., vol. 61, pages 1149-1159, 2005), regarding the impact of the protein sequence of a macromolecule on crystallization behavior:

> "Since the introduction of structural genomics, the protein has been recognized as the most important variable in crystallization." "Five naturally occurring variants, differing in 1-18 amino acids, of the 177-residue lectin domain of the F17G fimbrial adhesin were expressed and purified in identical ways. For four out of the five variants crystals were obtained, mostly in non-isomorphous space groups, with diffraction limits ranging between 2.4 and 1.1 Å resolution."

Specifically, the reference of Buts *et al.* teaches that the F17e-G and F17f-G adhesins differ in only one amino acid from the F17c-G adhesin, Arg21Ser and His36Tyr, respectively, and yet these proteins that are 99% identical in sequence resulted in different crystal forms with distinct diffraction properties (see Tables 1-3).

Additionally, the art of glycoprotein crystallography, as exemplified by López-Jaramillo *et al.* (Acta Crystallogr. F., vol. 61, pages 435-438, 2005), teaches how compositional heterogeneity in carbohydrate moieties of glycoproteins further complicates the time consuming and difficult task of obtaining diffraction quality crystals form a suitable source that would yield high resolution three-dimensional structures:

> "One of the lessons learnt from proteomics is that despite important advances in protein production, X-ray diffraction, phasing and refinement, success critically depends on the crystallization stage, where the **lack of knowledge is usually compensated for by massive screening** (i.e. brute force; Hui & Edwards, 2003; Rupp, 2003; Luft et al., 2003; De Lucas et al., 2003) or **by the manipulation of the protein to change its intrinsic characteristics by point mutation, truncations, deletions and fusion to other proteins** (Dale et al., 2003). The state of the art for the crystallization of glycoproteins is even worse. Little systematic work on the crystallization of glycoproteins has been carried out (Stura et al., 1992) and it represents a challenge since (i) natively glycosylated proteins cannot be produced in standard overexpression systems because the glycosylation pattern is not directly dependent on the genome but on the species and tissues, (ii) purification yields heterogeneous samples consisting of a mixture of molecules with partial deglycosylation of the carbohydrate fraction and (iii) carbohydrates can hinder the crystallization because they are flexible and can obscure a substantial fraction of the potential crystal contact- forming protein surface. This negative view of carbohydrates has led to suggestions of their removal from the protein, despite the fact that the carbohydrate fraction is an important piece of information (McPherson, 1999)"

Since our understanding of crystallization mechanisms are still incomplete and the factors of macromolecular structure that are involved in crystallization are poorly understood, to make the macromolecular crystals encompassed by the scope of the genus of all polypeptide variants encoded by at least one HLA Class II gene, the following must be clear: the preparation and chemical composition of the molecules to be crystallized –including the glycosylation state-, and the crystallization conditions, including methods and reagents used. Crystallization experiments must be done in order to empirically determine if a macromolecule will crystallize, and preliminary X-ray diffraction experiments must be done in order to determine if the crystalline macromolecule will diffract to the resolution required for analysis. In the event that the interaction with an anticancer compound is studied by exposing a suitable unliganded protein crystal to said anticancer compound, the art recognizes the specific conditions of a "crystal soak" as essential for obtaining diffraction-quality crystals. The reference of Skarzynski *et al.* (Acta Crystallogr. D., vol. 62, pages 102-107, 2006, underline added for emphasis) teaches:

> "Soaking of crystals in appropriate solutions containing active compounds is the fastest way of creating protein-ligand complexes for suitable crystal systems, but there are a number of issues related to this method". "(iii) Binding of potent compounds often causes conformational changes of the protein molecules and either complete or partial disruption of the crystal lattice. This effect can be very dependent on time and compound concentration. A number of initial trial soaking experiments are usually needed to establish conditions where compound binding is likely to occur without significantly deteriorating the diffraction properties of the crystal."

Once a suitable crystal form is found and quality X-ray diffraction data has been collected, an electron density map of the protein can be calculated from which a three-dimensional structure/model can be generated. Therefore, precise instruction about how to make macromolecular crystals suitable for structure determination is required so that undue

experimentation is not required. Thus, it is the Examiner's position that screening for suitable glycoforms encoded by HLA Class II genes leading to diffraction quality crystals, which might lead to a three-dimensional structure/model, would constitute undue experimentation.

In silico screening

At the time of the invention, *in silico* screening methods for identifying compounds that bind to a defined binding pocket were known in the art (see for example, Balaji *et al.* US Patent 5,579,250 and Itai *et al.* US Patent 5,642,292). While such methods of structure-based screening of compounds using defined target three-dimensional models representative of the natural state of the target are known in the prior art, knowledge of clearly defined target models for the claimed genus is lacking in the specification.

The existence of high-resolution three-dimensional structures of HLA Class II hetorodimers, which could be used for creating a homology model of an HLA Class II heterodimer containing identified polymorphic positions of β chain, are noted in the prior art. However, the instant claims read on using the structure of only the β chain of an HLA class II heterodimer. It is well established in the arts of *in silico* screening that obtaining a potential associating species without a clearly defined target three-dimensional model is highly unpredictable. That is, it would appear to be highly unpredictable as to whether all three-dimensional models of a polymorphic β chain of an HLA Class II gene having unrestricted structure and atomic composition, would be useful for identifying a compound that interact with a functional HLA Class II heterodimer. For example, said three-dimensional models would represent non-biologically-relevant representations of HLA Class II missing half of its peptide-

binding groove. It is highly unpredictable as to whether a compound that is identified as binding to such models as encompassed by the claims will also bind to the biologically relevant protein. Searching among any and all possible three-dimensional models for a target model that is suitable for the evaluation, identification or design of a compound is well outside the realm of routine experimentation and predictability in the art of success in is extremely low. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus of three-dimensional models in order to use such members.

The amount of direction provided by the inventor; The existence of working examples: Neither specific guidance nor working example are disclosed to determine the structure of a polypeptide using X-ray diffraction data or amino acid sequence data. In addition, there is no reduction to practice of the claimed screening method. It follows that without such direction in making a defined three-dimensional model, the specification lacks precise guidance for using the claimed invention.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: In order to practice the claimed invention one of skill in the art must generate three-dimensional protein structural variant models of β chain from either X-ray diffraction data or amino acid sequence data. For the reasons set forth above, there would be an unpredictable amount of experimentation required to practice the claimed invention.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior and current state of the art, and the amount of experimentation required to make all the

crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

NEW-Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior ad are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 11-14 are rejected under 35 U.S.C. 103(a) as being obvious over Davies *et al.* (J. Clinical Oncology, vol. 19, pp. 1279-1287, 2001) in view of Lee *et al.* (Gastroenterology, vol. 111, pp. 426-432, 1996).

Davies *et al.* teach a method for evaluating cancer treatments based on genotyping polymorphic genes of patients receiving cancer therapy and correlating the survival results of

patients containing a specific polymorphic gene with appropriate cancer treatment regimens (see abstract, p. 1279). The reference teaches that the polypeptides encoded by polymorphic genes of Glutathione S-transferase, i.e., namely theta (GSTT1) and mu (GSTM1), affect the cytotoxicity of chemotherapeutic drugs. Experimental DNA typing data of Glutathione S-transferase polymorphic genes were obtained from a patient population of children with acute myeloid leukemia or AML (see Table 1 and GST Genotyping, p. 1280) receiving chemotherapy (see Chemotheraphy Treatment Regimen). GSTT1 and GSTM1 genotype outcome differences in overall survival, disease-free survival and relapse-free survival were statistically analyzed (see Statistical Analysis, p 1280, Figures 1-5, pp.1281-1282, and Tables 2-3, pp.1282-1283) and further lead to the conclusion that children lacking GSTT1 had greater toxicity and reduced survival rate after chemotherapy for AML compared with children with at least one GSTT1 allele, wherein the genotype might be useful in selecting appropriate chemotherapy regimens for children with AML(see last paragraph of p. 1284).

Davies *et al.* do not teach any association of HLA class II genes with any cancer. However, the reference of Lee *et al.* teaches HLA Class II genes are associated with several cancers (see line 1-2, 1st column, p.426). Namely, "HLA-DQB1*0301 is more common in Caucasian patients with gastric adenocarcinoma than noncancer controls" (see conclusions, p. 426).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the genotyping methods of Davies *et al.* or Lee *et al* along with the statistical methods of Davies *et al.* to identify HLA Class II polymorphic genes of patients receiving any cancer therapy and correlating the survival results of HLA Class II genotype with appropriate

cancer treatment regimens. Because of the extensive cancer polymorphic genotyping of Lee *et al.* and the productive resultsof cancer polymorphic genotyping of Davies *et al.*, one would have been motivated by Davies *et al.,* who states that "This study shows that pharmacogenetic factors can influence the outcome of therapy, and particularly dose-intensive therapy".

B. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being obvious over Davies *et al.* (J. Clinical Oncology, vol. 19, pp. 1279-1287, 2001) in view of Lee *et al.* (Gastroenterology, vol. 111, pp. 426-432, 1996), Toh *et al.* (Protein Engineering, vol. 11, pp. 1027-1032, 1998), and Gibbs *et al.* (Science. Vol. 287, pp. 1969-1973, 2000).

The teachings of Davies *et al.* and Lee *et al.* are set forth above and reiterated herein as they apply to claim 1 (steps 1-3), namely the association of HLA Class II polymorphism with several cancer types and the correlation the survival results of cancer patients with a specific HLA Class II genotype, i.e. specific polymorphism, with appropriate cancer treatment regimens. However, these references do not teach a homology model of an HLA Class II polypeptide that could be used for *in silico* screening of compounds.

Toh *et al.* teach a homology model HLA Class II heterodimer, namely, HLA-DRB1*0405 (see p. 1027, 2nd column, preparation of input coordinates).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to evaluate a candidate therapy for cancer of associated with a polymorphic gene comprising *in silico* screening a compound (i.e. proteins, peptides, peptidomimetics, or small molecules) with a homology model consisting of a specific polymorphic HLA Class II polypeptide because it was well known in the art at the time the invention was made that the

HLA Class II polymorphic genes, such as HLA-DQB1*0301 of Lee *et al.*, were associated with several types of cancer, including adenocarcinomas of the stomach. One would have been motivated to do so because it is routine in the art of onco-pharmacological research to screen thousands of candidate therapeutics against gene targets known to be associated with tumors. Indeed, Gibbs *et al.* teaches (page 1970) that over the last 20 years, there has been a fundamental shift in the way target identification in cancer is approached. Advances in molecular biology now allow us to identify genes that go awry in cancer, and offer the opportunity to dissect the molecular mechanisms underlying the disease. Gibbs further teaches that the choice of the target is often highlighted by the mutated gene underlying the cancer (such as ras, p53, p16, myc) wherein overexpression of specific gene products, such as epidermal growth factor (EGF), insulin-like growth factor receptors, and cyclins, have correlated as a causative factor in some cancers. Gibbs further teaches that many molecular tools are available for target validation, including antisense oligonucleotides, ribozymes, dominant negative mutants, neutralizing antibodies, and mouse transgenics/knockouts. Gibbs also teaches that successful screening of compounds to molecular targets has resulted in the identification of new therapies now being realized on a large scale in the clinic (Table 1). However, Gibbs *et al.* is silent about *in silico* screening methods.

Because simply changing the screening method to be used is not beyond the ordinary skill in the art, the references, taken together, reasonably suggest to one of ordinary skill in the art would be motivated to use the homology modeling of Toh *et al.* to create a three-dimensional model of an HLA Class II heterodimer, either to screen for compounds that interact with a polymorphic HLA Class II polypeptide that has been associated with cancer or .to screen for

additional compounds that interact with a specific polymorphic HLA Class II polypeptide that has been correlated with a particular cancer treatment regimen.

Response to Arguments

21. The response filed on September 26, 2005 has been fully considered. All previous rejections and or objections are withdrawn in view of applicant's amendments and arguments there to. Note that new claim objections have been raised. Additionally, note that new grounds of rejections have been instituted under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 112 first paragraph and 35 U.S.C. § 103 for the reasons stated above.

Conclusion

Claims 1-14 and 19-24 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Miguel A. Talavera whose telephone number is (571)272-3354. The examiner can normally be reached on M-F, 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on (571)272-0931. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Miguel A. Talavera, Ph.D.
February 15, 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER